REMARKS

This is a response to the Office Action mailed October 9, 2002. Claims 1-6, 11-13, 21, 22, 24, 27 and 29-39 are pending in the application. Claims 1-6, 11-13 and 21-31 have been rejected by the Examiner. As noted above, Applicants have canceled Claims 7-10, 14-20, 23, 26 and 28, amended Claims 1-4, 11-13, 21, 22, 24 and 27 and submitted new Claims 32-39. The amendments and the new Claims 32-39 are fully supported by the written description. Also, no new matter has been introduced into the application.

Election/Restrictions

Applicants affirm election of Group I, Claims 1-6, 11-13 and 21-31. Claims 7-10 and 14-20 have been canceled without prejudice.

Claim Rejections – 35 U.S.C. § 103

The Examiner has rejected Claims 1-6, 11-13 and 21-31 under 35 U.S.C. §103(a) as being unpatentable over Roth et al. (USPN 5,837,313). Roth et al. is directed to a method of delivering bioactive molecules to cells. Roth et al. disclose that "encapsulation of nucleic acid molecules or biologically active proteins within biodegradable, biocompatible polymeric microparticles which are appropriate sized to infiltrate, but remain trapped within, the capillary beds and alveoli of the lungs can be used for targeted delivery to these regions of the body following administration to a patient by infusion or injection" (abstract).

1. CLAIMS 1-6.

In order to establish *prima facie* obviousness, **all of the claimed limitations must be taught or suggested** in the references cited. In re Royka, 490 F.2d 981. Roth et al. clearly fail to disclose a method of achieving a therapeutic effect that includes

> delivering a particle containing a therapeutic substance to an anatomical structure comprising a lumen **such that said particle forms an embolus within said lumen for a**

transitory period, said transitory period being less than seven days and less than the duration which results in cell damage or cell death; and

wherein said therapeutic substance is released from said particle, causing said therapeutic effect

as recited by amended Claim 1. In particular, Roth et al. fail to disclose that their microparticles are capable of forming emboli for a duration that is less than the duration which results in cell damage or cell death. Roth et al. do not even recognize the problem of cellular damage caused by microparticles that are lodged in the lumen for longer than seven days. The microparticles disclosed by Roth et al., therefore, are clearly not designed nor are they capable of degrading in **less than seven days and less than the duration which results in cell damage or cell death**.

The Examiner has acknowledged that Roth et al. do not teach that the microparticles form emboli for less than seven days. The Examiner takes the position, however, that "one of ordinary skill in the art would consider the time a manipulatable parameter, depending upon the active agent used and the desired effect." Applicants respectfully submit that the Examiner has relied on an improper basis for rejecting Claim 1. There is no case law that finds a prior art reference discloses a limitation, inherently or otherwise, merely because the limitation is directed to a "manipulatable parameter." Furthermore, patent law does not hold that a claim is obvious because one of ordinary skill in the art would consider a limitation to be a "manipulatable parameter." It appears that the Examiner has equated that which is within the capabilities of one skilled in the art with obviousness. However, this is not the law. The mere fact that one may argue that the prior art is capable of being modified to perform a claimed method does not by itself make the claimed method obvious. Applicants, therefore, respectfully request the Examiner to reconsider this basis for rejection of Claim 1.

Additionally, to the extent that the Examiner contends that the duration of blockage has merely been "optimized" by the Applicants, Applicants submit that they have clearly rebutted

this contention by showing that the duration is critical. In particular, the duration is critical to mitigate or prevent cellular damage or death.

In addition, Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness because there would have been no suggestion or motivation to modify Roth et al. in order to make the claimed invention. There must be a motivation provided by the prior art, and that motivation is totally lacking in the reference. Roth et al. do not recognize the problem of cellular damage caused by microparticles that are lodged in the lumen for longer than seven days, and in fact teach that the microparticles can be lodged for as long as **six months** (col. 4, line 38). This extremely long duration suggested by Roth et al. clearly teaches away from the limited duration of the present invention. Applicants respectfully request the Examiner to provide evidence from the prior art that one skilled in the art would have had motivation to modify Roth et al.

It is also clear that Roth et al. do not disclose all of the limitations of the claims that are dependent on amended Claim 1. For instance, Roth et al. fail to disclose a method of delivering a particle to an anatomical structure that has a first region and a second region branching from the first region which includes "occluding said first region at a position downstream of the location at which said second region branches from said first region; and introducing said particle into said first region upstream of the location at which said second region branches from said first region" as recited by amended Claim 2. In particular, Roth et al. fail to disclose or even suggest that a portion of the artery should be occluded before injecting the microparticles in order to direct the microparticles away from the occluded portion. Instead, Roth et al. merely disclose injecting the particles "into the artery feeding the affected limb or region" (col. 14, lines 38-39). The method of Roth et al., therefore, allows the microparticles that are injected to travel haphazardly through the artery as propelled by the blood flow without being directed to a particular target lumen. As a result, the microparticles can be propelled to unwanted regions of

the body. This disadvantage is clearly acknowledged by Roth et al. ("[i]t should be noted that some microparticles will probably exit the treated region, and lodge in the lungs or elsewhere") (col. 14, lines 42-44).

Accordingly, the Applicants respectfully request that the Examiner reconsider the finding of obviousness, and allow independent Claim 1. Since Claims 2-6 depend directly or indirectly on Claim 1, Claims 2-6 should also be allowable.

2. CLAIMS 11-13.

As noted above, in order to establish *prima facie* obviousness, **all of the claimed limitations must be taught or suggested** in the references cited. Roth et al. do not suggest or disclose a method of achieving a therapeutic effect comprising

> delivering a particle comprised of a biodegradable substance and a therapeutic substance to an anatomical structure including a lumen, said particle having a first diameter sufficient to form an embolus within said lumen at a first site; wherein said biodegradable substance is capable of degrading within said lumen to a second diameter smaller than the diameter of said lumen at said first site **in less than seven days to release said particle from said first site to mitigate or prevent cellular damage at said first site**

as recited by Claim 11. Roth et al. clearly fail to disclose that the "biodegradable substance is capable of degrading within said lumen to a second diameter smaller than the diameter of said lumen at said first site **in less than seven days** to release said particle from said first site." Instead, Roth et al. disclose that the particles are designed to persist for as long as **six months** (col. 4, line 38). The microparticles of Roth et al., therefore, are not designed nor are they capable of degrading in a less than seven days from the first site in order to **mitigate or prevent cellular damage** at the first site.

In addition, Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness because there would have been no suggestion or motivation to modify Roth et al. in order to make the claimed invention. The Examiner has stated that "one of

ordinary skill in the art would consider the time a manipulatable parameter, depending upon the active agent used and the desired effect." Thus, the Examiner equates that which is within the capabilities of one skilled in the art with obviousness. However, this is not the law. The mere fact that one may argue that the prior art is capable of being modified to perform a claimed method does not by itself make the claimed method obvious. There must be a motivation provided by the prior art, and that motivation is totally lacking in the reference. Roth et al. do not recognize the problem of cellular damage caused by microparticles that are lodged in the lumen for longer than seven days, and instead teach away from a limited duration by disclosing that the microparticles can be lodged for as long as **six months**. Accordingly, Claim 11 is allowable over Roth et al. Claims 12 and 13 depend directly or indirectly from Claim 11 and are allowable for at least the same reason.

3. CLAIMS 21-31.

Roth et al. also do not suggest or disclose a method of achieving a therapeutic effect within an anatomical structure having a first region and a second region, said second region being located downstream of said first region and having a smaller cross-sectional diameter than said first region, where the method comprises

> delivering a particle having a first size in which said particle is not capable of passing from said first region into said second region, **said particle comprising a water soluble polymer and a hydrophobic counterion**; and
>
> wherein said particle subsequently reduces from said first size to a smaller second size as said particle travels through said anatomical structure, allowing said particle to pass into said second region

as recited by Claim 21. In particular, Roth et al. at least do not disclose "delivering a particle having a first size in which said particle is not capable of passing from said first region into said second region, **said particle comprising a water soluble polymer and a hydrophobic counterion**." Accordingly, Claim 21 is allowable over Roth et al. Claims 22, 24, 27 and 29-31

depend directly or indirectly from Claim 21 and are allowable for at least the same reason.

Claims 23, 26 and 28 have been canceled without prejudice.

CONCLUSION

Claims 1-6, 11-13, 21, 22, 24, 27 and 29-39 are pending in this application. Examination and allowance of the claims are respectfully requested. If the Examiner has any questions or concerns, the Examiner is invited to telephone the undersigned attorney at (415) 954-0323.

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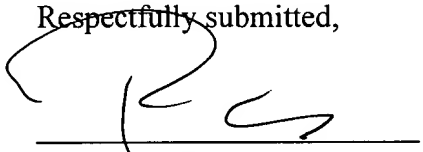
Respectfully submitted,



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Version With Markings To Show Changes Made

IN THE SPECIFICATION

The paragraph beginning on page 14, line 21 has been amended as follows:

Hydrolysis is the mechanism by which many bioerodable polymers, including polyesters, polyanhydrides, and ~~**polyphosphazenes**~~**polyphosphazines**, erode. Most such materials erode over a period of days to months and, as such, are too long-lived for use in accordance with some embodiments in the present disclosure.

IN THE CLAIMS

Please amend the Claims as noted below. The italicized claims are the remaining claims which have not been amended and are provided for the Examiner's reading convenience.

1. (Amended) A method of achieving a therapeutic effect comprising:

~~providing~~**delivering** a particle containing a therapeutic substance to an anatomical structure comprising a lumen such that said particle ~~embolizes~~**forms an embolus** within said lumen for a transitory period ~~of less than one week;~~**, said transitory period being less than seven days and less than the duration which results in cell damage or cell death; and**

wherein said therapeutic substance is released from said particle, causing said therapeutic effect.

2. (Amended) The method of Claim 1, wherein said anatomical structure has a first region and a second region branching from said first region, said second region being located downstream from said first region, and wherein said ~~providing~~**delivering** a particle to an anatomical structure comprises the acts of:

~~causing an occlusion in~~**occluding** said first region at a position downstream of the location at which said second region branches from said first region; and

introducing said particle into said first region upstream of the location at which said second region branches from said first region.

3. (Amended) The method of Claim 1, wherein said anatomical structure has a first region and a second region branching from said first region, said second region being located downstream from said first region, and wherein said ~~providing~~**delivering** a particle to an anatomical structure comprises the acts of:

occluding said first region at positions both upstream and downstream of the location at which said second region branches from said first region; and

introducing said particle into said first region between the upstream and downstream occlusions.

4. (Amended) The method of Claim 1, wherein said lumen contains an occlusion therein and wherein said ~~providing~~**delivering** a particle to an anatomical structure comprises the act of:

introducing said particle into said lumen upstream of said occlusion.

5. *The method of Claim 4, wherein said therapeutic substance is an angiogenic substance and wherein said therapeutic effect is collateral growth upstream of said occlusion.*

6. *The method of Claim 1, wherein said particle reduces in size as said therapeutic substance is released therefrom.* Please cancel Claims 7-10.

11. (Amended) A method of achieving a therapeutic effect comprising~~:providing~~ **delivering** a particle **comprised of a biodegradable substance and a therapeutic substance** to an anatomical structure ~~having~~**including** a lumen ~~such that said particle embolizes within said lumen for a transitory period;~~

~~wherein said transitory period of embolization causes a brief period of reduced blood flow through said lumen that induces a therapeutic bodily response~~, **said particle having a first diameter sufficient to form an embolus within said lumen at a first site; wherein said biodegradable substance is capable of degrading within said lumen to a second diameter smaller than the diameter of said lumen at said first site in less than seven days to release said particle from said first site to mitigate or prevent cellular damage at said first site**.

12. (Amended) The method of Claim 11, wherein **delivering** said ~~act of providing a~~ particle to said anatomical structure comprises the act of delivering pulses of said particles to said anatomical structure.

13. (Amended) The method of Claim 12, wherein the act of delivering pulses of said particles causes a series of ~~said~~ brief periods of reduced blood flow~~; wherein said therapeutic bodily response induced by said series of brief periods of reduced blood flow is~~ thereby causing collateral growth at said first site.

Please cancel Claims 14-20.

21. (Amended) A method of achieving a therapeutic effect within an anatomical structure having a first region and a second region, said second region being located downstream of said first region and having a smaller cross-sectional diameter than said first region, the method comprising ~~the acts of~~:

~~(a) providing~~delivering a particle having a first size in which said particle is not capable of passing from said first region into said second region, said particle ~~being capable of reducing in size;~~comprising a water soluble polymer and a hydrophobic counterion; and

~~(b) delivering said particle having said first size to said first region of said anatomical structure;~~

wherein said particle subsequently reduces from said first size to a smaller second size as said particle travels through said anatomical structure, allowing said particle to pass into said second region~~; and~~

~~wherein a therapeutic effect is achieved~~.

22. (Amended) The method of Claim 21, wherein said particle includes a therapeutic substance~~; wherein said therapeutic substance~~ that is released from said particle~~; and wherein~~ in said ~~therapeutic effect results from said therapeutic substance~~anatomical structure.

Please cancel Claim 23.

24. (Amended) The method of Claim ~~23,~~21, wherein said particle ~~includes a therapeutic substance and wherein said transitory~~reduces from said first size to said smaller second size in a period ~~is~~of less than one week;

~~wherein said therapeutic substance is released from said particle; and~~

~~wherein said therapeutic effect results from said therapeutic substance~~ thereby mitigating or preventing cellular damage at said first site.

Please cancel Claim 26.

27. (Amended) The method of Claim 21, wherein during said act of traveling through said anatomical structure, said particle becomes transiently lodged in a plurality of locations throughout said anatomical structure as said particle reduces in size over a period of ~~days~~less than one week, providing ~~said~~a therapeutic effect over a length of said anatomical structure.

Please cancel Claim 28.

29. *The method of Claim 21, wherein said anatomical structure comprises a single lumen containing said first region and said second region.*

30. *The method of Claim 21, wherein said anatomical structure comprises a lumen network including a plurality of lumens.*

31. *The method of Claim 21, wherein said anatomical structure additionally includes a third region, said third region being located downstream of said second region and having a smaller cross-sectional diameter than said second region;*

wherein said particle is capable of reducing from said second size to a smaller third size, allowing said particle to pass from said second region into said third region.

Please add the following new claims:

32. (New) A method of releasing a therapeutic substance in a lumen comprising delivering a particle comprised of a biodegradable compressed material and a therapeutic

substance to a lumen, said particle having a first diameter sufficient to form an embolus within said lumen at a first site.

33. (New) The method of Claim 32, wherein said biodegradable substance is capable of degrading within said lumen to a second diameter smaller than the diameter of said lumen at said first site in less than seven days to release said particle from said first site thereby mitigating or preventing cellular damage at said first site.

34. (New) A method of delivering a therapeutic substance to a lumen network, said lumen network having a plurality of branched lumens, said method comprising:

occluding a portion of said lumen network; and

delivering a particle to a lumen in said lumen network upstream of said occlusion, the particle comprising a biodegradable substance, wherein said occlusion prevents said particle from entering said portion of said lumen network.

35. (New) A method of delivering a biodegradable substance to a lumen network, the lumen network having a first region and a second region branching from said first region downstream from said first region, wherein said second region has a first branch and a second branch, said method comprising:

occluding said first branch of said second region; and

delivering a particle to said first region upstream of said occlusion, the particle comprising a biodegradable substance and having a first diameter sufficient to form an embolus within said second branch of said second region.

36. (New) The method of Claim 35, additionally comprising occluding said first region, wherein said particle is delivered between the upstream and downstream occlusions.

37. (New) The method of Claim 35, wherein said particle further comprises an angiogenic substance and wherein said angiogenic substance promotes collateral growth upstream of said occlusion.

38. (New) The method of Claim 35, wherein said particle further comprises a therapeutic substance and wherein said particle releases said therapeutic substance as said particle degrades.

39. (New) The method of Claim 35, wherein said biodegradable substance is capable of degrading within said second branch of said second region to a second diameter smaller than the diameter of said second branch in less than seven days to release said particle from said second branch thereby mitigating or preventing cellular damage at said second branch.

IN THE ABSTRACT

The Abstract has been amended as follows:

Compositions and methods of using the compositions to achieve a therapeutic effect are provided. ~~The compositions include a particle suitable for introduction into an anatomical structure and capable of reducing in size. In some embodiments, the particle contains a therapeutic substance and is capable of embolizing within the lumen for a transitory period of less than one week. The therapeutic substance is released from the particle as the particle reduces in size. In other embodiments, the particle is capable of embolizing within the lumen for a transitory period, causing a brief period of reduced blood flow which induces a therapeutic bodily response.~~

~~One method of achieving a therapeutic effect includes providing a particle containing a therapeutic substance to an anatomical structure having a lumen such that the particle embolizes within the lumen for a transitory period of less than one week. The therapeutic substance is released from the particle as the particle reduces in size, causing a therapeutic effect. Another method includes providing a particle to an anatomical structure having a lumen such that the particle embolizes within the lumen for a transitory period. The transitory period of embolization causes a brief period of reduced blood flow through the lumen that induces a therapeutic bodily response.~~

~~Also provided is a method of achieving a therapeutic effect within an anatomical structure having a first region as well as a second region located downstream of the first region and having a smaller cross-sectional diameter than the first region.~~